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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BROWE, DAVID	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
02/15/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomail@panitchlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/598,212	DYER ET AL.	
	Examiner	Art Unit	
	DAVID BROWE	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1,7-13,15-27 and 36-41* is/are pending in the application.

5a) Of the above claim(s) *24-27 and 36-41* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1, 7-13, and 15-23* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *21 August 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed November 12, 2010, that includes a response to the Final Office Action mailed August 13, 2010, has been entered. Claims 1 and 18-19 have been amended; claims 2-6, 14, and 28-35 have been canceled; and claims 36-41 have been newly added. Claims 24-27 stand withdrawn. Claims 36-41 are withdrawn as being directed to non-elected subject matter (i.e. process of use). Claims 1, 7-13, and 15-23 are currently under examination.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 7-13, and 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chenite *et al.* (U.S. Patent No. 6,344,488), in view of Dunn *et al.* (U.S. Patent No. 5,702,716) and Illum (U.S. Patent No. 5,629,011).

Applicant Claims

Applicants claim a nasal or ocular delivery composition in the form of an aqueous solution or suspension for delivery in the form of a spray or drops of a therapeutic agent across a mucosal surface into an animal's systemic circulation comprising: *a)* chitosan, a salt thereof, or a derivative thereof that has been formed by bonding of acyl or alkyl groups with the hydroxyl groups of the chitosan; *b)* a polyol-phosphate or sugar-phosphate salt; *c)* triethyl citrate, as a plasticizer; and *d)* a systemically-acting therapeutic agent. The chitosan, or derivative or salt thereof, has a molecular weight of

4,000 Da. or greater, particularly 50,000-300,000 Da; a degree of deacetylation of 40% or greater, particularly 70-90%; comprises from 0.25-3.0% to 0.45-1.5% w/v of the composition; and can be a chitosan base; or a nitrate, phosphate, sulphate, citrate, hydrochloride, glutamate, lactate, or acetate salt of chitosan. The polyol-phosphate or sugar-phosphate salt is β-glycerophosphate disodium; and comprises from 0.25-3.0% to 0.75-2.0% w/v of the composition. Triethyl citrate comprises from 0.05-5.0% to 0.2-1.0% w/v of the composition. The therapeutic agent is a polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-6-glucuronide. The composition further comprises 0.01-0.2% w/v ascorbic acid. The animal is a human.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Chenite *et al.* disclose an ophthalmic (i.e. ocular) delivery composition comprising: *a)* chitosan, or a derivative or salt thereof, *b)* a polyol-phosphate or sugar-phosphate salt, and *c)* a systemically-acting therapeutic agent (Col. 3, lns. 5-8, 14-25, 62-64; Col. 4, lns. 5-6, 30-31; Col. 5, lns. 65-66), and further disclose that nasal peptide delivery can also be effected by chitosan-based drug delivery systems (Col. 1, lns. 47-50; Col. 2, lns. 19-21; Col. 5, lns. 1-2). The composition is in the form of an aqueous solution or suspension at room temperature and upon ocular or body cavity administration to an animal (Col. 4, lns. 40-44; Col. 5, lns. 1-2; Col. 6, lns. 1-3; Col. 10,

lns. 5-9; Col. 11, lns. 17-20, 28-31). The chitosan, or derivative or salt thereof, has a molecular weight of 4,000 Da. or greater, particularly 50,000-300,000 Da; comprises from 0.25-3.0% to 0.45-1.5% w/v of the composition; and can be a chitosan base or derivative formed by bonding of acyl or alkyl groups with the hydroxyl groups of the chitosan or a nitrate, phosphate, sulphate, citrate, hydrochloride, glutamate, lactate, or acetate salt of chitosan (Col. 3, lns. 16-17; Col. 4, lns. 45-46; Col. 7, lns. 7-10). The chitosan deacetylation degree and molecular weight employed, and the solution pH all greatly influence the solution properties, such as viscosity, as well as the gelation time at a particular temperature, and can be adjusted as desired through routine optimization (Col. 7, lns. 4-6, Col. 9, lns. 11-55; Col. 12, lns. 22-25, 29-33). The polyol-phosphate or sugar-phosphate salt is β-glycerophosphate disodium; and comprises from 0.25-3.0% to 0.75-2.0% w/v of the composition (Col. 3, lns. 18-21, 50-56). The therapeutic agent is a polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-6-glucuronide (Col. 13, lns. 9-22). The composition further comprises ascorbic acid (Col. 4, lns. 35-40). The animal is a human (abstract).

Dunn *et al.* disclose a nasal or ocular delivery composition in the form of a solution or suspension for delivery, by any suitable method for applying a liquid (i.e. such as spray or drops), of a therapeutic agent across a mucosal surface into an

animal's systemic circulation comprising: *a)* a thermoplastic polymer; *b)* triethyl citrate, as a plasticizer; and *c)* a systemically-acting therapeutic agent (Col 1, lns. 65-67; Col. 2, lns. 1-12, 15-30; Col. 3, lns. 35-43, 50-57; Col. 4, lns. 18, 31; Col. 8, lns. 19, 26, 31; Col. 10, lns. 1-47, 66; Col. 11, lns. 1-24). The thermoplastic polymer is chitosan; and has a molecular weight preferably between 15,000-100,000 Da (Col. 4, lns. 19, 31; Col. 5, lns. 59-61; Col. 6, lns. 43-56). Triethyl citrate comprises from 0.05-5.0% to 0.2-1.0% w/v of the composition (Col. 8, lns. 19, 26, 31, 43-53). The therapeutic agent is a polar drug, insulin or other polypeptide, calcitonin or other hormone (i.e. such as leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor) (Col. 10, lns. 1-67; Col. 11, lns. 1-24).

Illum discloses a nasal delivery composition in the form of an aqueous solution or suspension specifically for delivery in the form of a spray of a therapeutic agent across a mucosal surface into an animal's systemic circulation comprising: *a)* chitosan, a salt thereof, or a derivative thereof that has been formed by bonding of acyl or alkyl groups with the hydroxyl groups of the chitosan; and *b)* a therapeutic agent intended for systemic action (abstract; Col. 1, lns. 4-6, 60-67; Col. 2, lns. 58-61, 66-67; Col. 3, lns. 1, 14-28, 55-58; Col. 8, lns. 50-53). The chitosan, or derivative or salt thereof, has a molecular weight of 4,000 Da. or greater, particularly 50,000-300,000 Da; a degree of deacetylation of 40% or greater, particularly 70-90%; comprises from 0.25-3.0% to 0.45-1.5% w/v of the composition; and can be a chitosan base; or a nitrate, phosphate, sulphate, citrate, hydrochloride, glutamate, lactate, or acetate salt of chitosan (Col. 3, lns. 27-28, 55-58, 67; Col. 4, lns. 1-7; Col. 6, lns. 32-33). The therapeutic agent is a

polar drug, a polypeptide, a gene or a gene construct, insulin, calcitonin, leuprolide, luteinizing hormone releasing hormone, growth hormone or a growth hormone releasing factor, naratriptan, sumatripan, zolmitriptan, rizatriptan, eletriptan, frovatriptan, alnitidan, avitriptan, almotriptan, apomorphine, sildenafil, alprostadil, diamorphine, hydromorphine, buprenorphine, fentanyl, oxycodone, codeine, morphine, or morphine-6-glucuronide (abstract; Col. 1, lns. 4-6, 60-67; Col. 8, lns. 65-67).

Ascertainment of the Difference Between the Scope of the Prior Art and the Claims (MPEP §2141.012)

Chenite *et al.* do not explicitly disclose the incorporation of triethyl citrate, as a plasticizer, into the composition, and that the composition is specifically a nasal delivery composition in the form of a spray. These deficiencies are cured by the teachings of Dunn *et al.* and Illum.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of the present invention to combine the respective teachings of Chenite *et al.*, Dunn *et al.*, and Illum, outlined *supra*, to arrive at Applicants claimed nasal or ocular delivery composition. Chenite *et al.* disclose ocular delivery composition in the form of an aqueous solution containing chitosan and active therapeutic agents that can be administered by any known means to an ophthalmic or other body cavity where they form sustained-release gels *in situ*. Since Dunn *et al.* disclose nasal and ocular delivery compositions in the form of an aqueous solution containing chitosan that preferably

incorporate triethyl citrate, as a plasticizer, to provide significantly improved control of its sustained-release character by causing the formation of a heretofore unknown distinctive macromolecular structure (Col. 3, lns. 50-57; Col. 7, lns. 8-11, 16, 59-63), one of ordinary skill in the art would be motivated to employ triethyl citrate in the composition of Chenite *et al.*, with the reasonable expectation that the resulting composition will successfully provide the means to fine-tune and significantly improve control of the desired therapeutic agent release rate of the composition *in situ.* Further, since Illum discloses that chitosan-based aqueous solutions for systemic delivery of active therapeutic agents (i.e. whereby chitosan serves as an absorption promoting agent to facilitate trans-mucosal passage of the active therapeutic agent from the gel into the systemic circulation) can be advantageously administered by the nasal route in the form of a spray, one of ordinary skill in the art would be motivated to employ in the composition of Chenite *et al.* as a nasal delivery composition in the form of a spray, with the reasonable expectation that the said composition will successfully provide sustained delivery of an effective amount of the systemically-acting active agent by the nasal route.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments filed November 12, 2010 have been fully considered but they are not persuasive.

i) Applicants contend that neither of the cited references, considered individually, fully discloses Applicants' claimed invention.

The Examiner, however, would like to point out that Applicants' claims have been rejected under 35 USC 103(a), not 35 USC 102, based on a combination of references, and what these references disclose or would have reasonably suggested to one of ordinary skill in the art. It has long been established that one cannot show nonobviousness by attacking references individually where the rejection is based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

ii) Applicants contend that the Chenite and Dunn references are concerned with compositions used as implants rather than as sprays or drops.

The Examiner, however, would like to point out in the first instance that the Illum reference explicitly discloses nasal delivery compositions comprising chitosan and active agent in the form of an aqueous solution or suspension for delivery in the form of a spray. Both the Chenite and Dunn references also disclose nasal and/or ocular delivery compositions that comprise chitosan and active agent, both are in the form of an aqueous solution or suspension for initial delivery to the nose or eye; and both are

said to be administered by any suitable method for applying a liquid. It would follow from the disclosure of Illum that these compositions can be delivered by spray; and, as any person of ordinary skill in the art would readily know, liquid solutions and suspensions can be and are routinely delivered as a spray or drop into the nose or eye. Finally, it should also be noted that the intended use "for delivery in the form of a spray or drops" is not even a limitation that carries patentable weight in this case.

iii) Applicants contend that the 1.132 Declaration of Peter James Watts, filed November 12, 2010, establishes that "*the use of triethyl citrate in the compositions of the present invention provides surprising and unexpected results*".

Respectfully, however, the Examiner cannot agree, for the following reasons:

a) the 1.132 Declaration as filed is in improper form. A proper 1.132 Declaration is in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims, and the evidence relied upon should establish that a significant aspect of the claimed invention would have been unexpected, and the differences in the results are statistically significant. At the very least, a comparison of the claimed invention with the Dunn composition containing triethyl citrate (i.e. commensurate in scope) should have been made, and the comparison should have resulted in statistically significant evidence that establishes that a significant aspect of the claimed invention is unexpected in light of the disclosure and teachings of Dunn. This was not done.

b) Dunn *et al.* disclose nasal and ocular delivery compositions in the form of an aqueous solution containing chitosan that *preferably incorporates triethyl citrate, as a*

plasticizer, to provide significantly improved control of its sustained-release characteristics. The Dunn composition is an aqueous solution at the time of administration, and exhibits a rapid increase in viscosity at physiological temperatures (i.e. upon delivery to the nose, eye, or other internal body site) to quickly form a matrix gel. It cannot be admitted that there is anything novel or unexpected about a nasal/ocular delivery composition in the form of an aqueous solution that combines chitosan with a plasticizer. It cannot be admitted that there is anything novel or unexpected about choosing triethyl citrate as the particular plasticizer. Not only is triethyl citrate one of the most commonplace and routinely used plasticizers, it is explicitly disclosed as being a *preferred* plasticizer by Dunn. Applicants have provided no evidence whatsoever that their claimed composition behaves in a superior or unexpected manner, or even any differently at all, compared to the Dunn composition. If anything, the 1.132 Declaration provides results using triethyl citrate that are expected, not unexpected, in view of Dunn.

For the foregoing reasons, and the reasons already of record, the 35 USC 103(a) rejection of claims 1, 7-13, 15-23, and 36-41 is hereby maintained.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DAVID BROWE whose telephone number is (571)270-1320. The examiner can normally be reached on Monday-Friday 8:30AM-6PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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